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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/552,287	01/04/2007	Anthony Futerman	30227	6293

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EXAMINER	
STEADMAN, DAVID J	

ART UNIT	PAPER NUMBER
1656	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/552,287	FUTERMAN ET AL.	
	Examiner	Art Unit	
	David J. Steadman	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 August 2009 and 19 November 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *123,124,129 and 133-158* is/are pending in the application.

4a) Of the above claim(s) *139-156* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *129,133-138,157 and 158* is/are rejected.

7)☒ Claim(s) *123 and 124* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *04 October 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

[1] A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/10/09 has been entered.

[2] Claims 123-124, 129, and 133-158 are pending in the application.

[3] Applicant's amendment to the claims, filed on 8/10/09, is acknowledged. This listing of the claims replaces all prior versions and listings of the claims.

[4] Applicant's amendment to the specification, filed on 8/10/09, is acknowledged.

[5] Receipt of a substitute Declaration under 37 CFR 1.63, filed on 8/10/09, is acknowledged.

[6] Receipt of a substitute sequence listing in computer readable form (CRF), a paper copy thereof, a statement of their sameness, and a statement that no new matter has been added to the specification by the paper copy of the sequence CRF, all filed on 11/19/09, is acknowledged.

[7] Applicant's remarks filed on 8/10/09 in response to the Office action mailed on 7/24/09 have been fully considered and are deemed to be persuasive to overcome at least one of the rejections and/or objections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

[8] The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Election/Restriction

[9] Claims 139-156 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made without traverse in the reply filed on 6/2/08.

Claim to Foreign Priority

[10] Applicant's claim to priority has been changed in view of the instant specification amendment. The instant application is a national stage filing under 35 U.S.C. 371 of PCT/IL04/00335. Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d) to Israel application 156273, filed on 6/2/03. The certified copy of the foreign priority document has been filed in the instant application on 10/4/05.

While the foreign priority document appears to provide descriptive support for the limitations of claims 123-124 and 129, the examiner can find no support for the limitations of claims 133-138 in the foreign priority document. Accordingly, claims 123-124 and 129 are accorded a priority date of 6/2/03, while claims 133-138 are accorded a priority date of 4/18/04.

Specification/Informalities

[11] In order to perfect compliance with the rules for a sequence listing, applicant is required to submit a formal amendment to the specification in accordance with 37 CFR 1.121, directing entry of the substitute sequence listing paper copy filed on 11/19/09 into the application. See the "Notice to Comply" mailed on 10/20/09, which indicates that applicant must provide an amendment directing the entry of the substitute sequence listing into the specification.

Claim Objections

[12] The objection to claim 134 in the recitation of "glycosylation moiety" is withdrawn in view of the instant claim amendment to claim 134 to delete the phrase at issue.

[13] Claims 123 and 129 are newly objected to in the recitation of "glucocerebrosidase molecule consisting of the amino acid sequence as set forth in SEQ ID NO:1…is glycosylated at asparagine 19 of said amino acid sequence" (claim 123) and "wherein substantially each of said glucocerebrosidase molecules...consists of the amino acid sequence as set forth by SEQ ID NO:1...is glycosylated at asparagine 19 of said amino acid sequence; and…is unglycosylated…" (claim 129). The transitional phrase "consisting of" excludes any element not specified in the claim (MPEP 2111.03) and because asparagine 19 is glycosylated, the recited glucocerebrosidase molecules cannot *consist* of the amino acid sequence of SEQ ID NO:1. In order to improve claim form, it is suggested that the noted phrase in claim 123 be amended to recite, *e.g.,* "glucocerebrosidase molecule, wherein the amino acid sequence of said

glucocerebrosidase molecule consists of SEQ ID NO:1…is glycosylated at asparagine 19 of said amino acid sequence" and the noted phrase in claim 129 be amended to recite, *e.g.,* "wherein the amino acid sequence of said glucocerebrosidase molecules consists of SEQ ID NO:1 and wherein substantially each of said glucocerebrosidase molecules is glycosylated at asparagine 19 and is unglycosylated".

[14] Claims 123 and 129 are newly objected to in the recitation of "glycosylation residues corresponding to Asn59…" Because the amino acid sequence recited in claims 123 and 129 is limited to consisting of SEQ ID NO:1, in order to improve claim form it is suggested that the noted phrase be amended to delete "corresponding to".

[15] Claim 134 is newly objected to in the recitation of "said asparagine 19 has at least one exposed mannose residue" and in order to improve claim form, it is suggested that the noted phrase be amended to recite, *e.g.,* "said asparagine 19 has an N-linked oligosaccharide with at least one exposed mannose residue".

Claim Rejections - 35 USC § 112, First Paragraph

[16] The written description rejection of claim(s) 123-124, 129, and 133-138138 under 35 U.S.C. 112, first paragraph, is withdrawn upon further consideration and in view of the instant claim amendment.

[17] The scope of enablement rejection of claims 123-124, 129, and 133-135 under 35 U.S.C. 112, first paragraph, is withdrawn upon further consideration and in view of the instant claim amendment.

[18] The scope of enablement rejection of claims 136-138 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and the reasons set forth below. The rejection was fully explained in a prior Office action. See, *e.g.,* [24] beginning at p. 13 of the Office action mailed on 9/17/08.

RESPONSE TO ARGUMENT: Beginning at p. 10 of the instant remarks, applicant argues the rejection is obviated by the instant amendment to claim 129 to limit the amino acid sequence and the site of glycosylation to asparagine 19.

Applicant's argument is not found persuasive. According to MPEP 2164.01(c), "When a compound or composition claim is limited by a particular use, enablement of that claim should be evaluated based on that limitation. See In re Vaeck, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991)". Claim 136 (claim 137 dependent therefrom) and 138 recite the intended use limitation "for treating a disease associated with glucocerebrosidase deficiency" and thus the enablement of the claimed pharmaceutical composition and article of manufacture is evaluated for the intended use of treating *any* disease associated with glucocerebrosidase deficiency. The phrase "disease associated with glucocerebrosidase deficiency" has been broadly and reasonably interpreted as encompassing diseases that are, *e.g.,* caused by glucocerebrosidase deficiency or have a symptom of glucocerebrosidase deficiency.

The nature of the invention is the treatment of Cerezyme®, a glucocerebrosidase which is glycosylated at Asn19, Asn59, Asn146, and Asn270 with peptide N-glycosidase F (PNGase F), which results in deglycosylation at Asn59, Asn146, and Asn270 while retaining the N-linked oligosaccharide at Asn19. The state of the prior art acknowledges the use of glucocerebrosidases including Cerezyme® for enzyme replacement therapy for treatment of Gaucher's disease. However, Tayebi et al. (*Mol. Genet. Metabol.* 79:104-109, 2003) acknowledges that parkinsonism associated with Gaucher's disease is refractory to enzyme replacement therapy (p. 105, column 1, middle). As such, one of skill in the art would recognize that it is highly unlikely that the claimed pharmaceutical composition and article of manufacture is useful for treating *any* "disease associated with glucocerebrosidase deficiency" and the specification fails to provide guidance or direction regarding those diseases that are and are not likely to be treated using the claimed pharmaceutical composition and article of manufacture. As such, the specification fails to enable the full scope of claimed pharmaceutical compositions and article of manufactures.

Claim Rejections - 35 USC § 102/103

[19] The rejection of claim(s) 133-137 under 35 U.S.C. 102(a) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Dvir (cited as reference U in the Form PTO-892 mailed on 9/17/08) is withdrawn in view of the petition under 37 CFR 1.48(a) to correct inventorship (hereafter "1.48(a) Petition), filed on 8/10/09 and further

in view of the Declaration under 37 CFR 1.132 (hereafter 132 Declaration), filed on 8/10/09.

The inventive entity as set forth in the Declaration under 37 CFR 1.63, filed on 10/4/05 is co-inventors Futerman, Sussman, Silman, Harel, Dvir, Toker, and Adamsky.

Regarding the 1.48(a) Petition, in view of the papers filed 8/10/09, it has been found that this nonprovisional application, as filed, through error and without deceptive intent, improperly set forth the inventorship, and accordingly, this application has been corrected in compliance with 37 CFR 1.48(a). The inventorship of this application has been changed by deleting as Swetlana Adamsky as a co-inventor. The application will be forwarded to the Office of Initial Patent Examination (OIPE) for issuance of a corrected filing receipt, and correction of Office records to reflect the inventorship as corrected.

According to the 132 Declaration, Andrew A. McCarthy is listed as a co-author of the reference of Dvir and “was listed on said article solely for his technical efforts…and was not a co-inventor". As such, the reference of Dvir is applicant’s own work, is not "by another", and is thus not available as prior art under 35 U.S.C. 102.

Claim Rejections - 35 USC § 103

[20] The rejection of Claim 138 under 35 U.S.C. 103(a) as being unpatentable over Dvir is withdrawn in view of the filing of the 1.48(a) Petition and 132 Declaration as noted above.

[21] Claims 129, 133-138, and 157-158 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over Roeber et al. (*Acta Cryst.* D59:343-344, 2003; reference 3 of the IDS filed on 6/27/07; hereafter "Roeber" in view of Grueninger-Leitch et al. (*Protein Science* 5:2617-2622, 1996; hereafter "Grueninger-Leitch") and Mills et al. (*Tetrahedron: Asymmetry* 11:75-93, 2000; hereafter "Mills"). The instant rejection is applied in view of the newly identified references to Grueninger-Leitch and Mills.

CLAIM INTERPRETATION: The following remarks are provided to clarify the examiner's interpretation of the claimed subject matter. Regarding claim 129, it is noted that the recited glucocerebrosidase polypeptide is limited to consisting of the amino acid sequence of SEQ ID NO:1. According to the specification at p. 74, lines 8-10, "Cerezyme® is a human glucocerebrosidase molecule having an amino acid sequence set forth by SEQ ID NO:1…" The glucocerebrosidase of claim 129 is limited to being glycosylated at asparagine 19 and deglycosylated at asparagines 59, 146, and 270, which, according to the specification at p. 93, lines 5-7, appears to be an inherent feature of treating Cerezyme® with peptide N-glycosidase F (PNGase F). Also, the glucocerebrosidase of claim 129 is limited to being "able to form pure glucocerebrosidase crystals...", which is interpreted as an intended use of the recited glucocerebrosidase polypeptide.

Regarding claim 133, the claim limits the glucocerebrosidase to having "about the same capacity to catalyze hydrolysis of a glucocerebrosidase as a population of fully glycosylated glucocerebrosidase molecules…", which is interpreted as an inherent feature of the glucocerebrosidase of claim 129.

Regarding claim 135, the claim limits at least some of the glucocerebrosidase molecules to being "capable of being internalized by a phagocyte", which is interpreted as an inherent feature of the glucocerebrosidase of claim 129.

Regarding claim 136-137, the "pharmaceutical composition" is broadly and reasonably interpreted as encompassing a buffered solution of the recited glucocerebrosidase with the recitation of "for treating a disease…" being an intended use limitation.

Regarding claim 138, the "article of manufacture" is broadly and reasonably interpreted as encompassing a container comprising a solution of the recited glucocerebrosidase with the recitation of "the article of manufacture being identified for treatment of a disease…" being an intended use limitation.

Regarding claim 157, the claim limits the glucocerebrosidase to having "normal enzymatic activity compared to a population of fully glycosylated glucocerebrosidase molecules…", which is interpreted as an inherent feature of the glucocerebrosidase of claim 129.

Regarding claim 158, the recitation of "for treating Gaucher's disease…" being an intended use limitation.

The reference of Roeber teaches Cerezyme® is a glycoprotein (p. 343, column 2, top) and further teaches crystallization of Cerezyme® (p. 343, column 2, bottom to p. 344, column 1, bottom). Roeber does not teach a solution of Cerezyme® treated with PNGase F.

However, the reference of Grueninger-Leitch teaches deglycosylation of native glycoproteins using recombinant PNGase F with subsequent removal of the recombinant PNGase F (p. 2617, abstract and p. 2621, column 1, bottom). Grueninger-Leitch teaches the glycan moiety of glycoproteins influences crystallography and that deglycosylation prior to crystallization may offer the key to obtaining high quality crystals (p. 2617, column 1). According to Grueninger-Leitch, the results confirm the notion that deglycosylation should be used as a routine method in screening for crystallization conditions. Grueninger-Leitch teaches it is not necessary that deglycosylation be complete because removal of a subset of glycans may already bring an improvement of crystallizability or crystal quality (p. 2620, paragraph bridging columns 1-2). Grueninger-Leitch does not expressly teach Cerezyme® for deglycosylation of PNGase F.

However, Mills teaches Cerezyme® has five potential glycosylation sites at positions 19, 59, 146, 270, and 462 and expressly teaches treatment of an iodoacetamide-derivatized Cerezyme® with PNGase F is successful in removing glycans (p. 85, see 4.5). According to Mills, the combined results indicate that four of the five sites are glycosylated with the fifth position, 462, being unglycosylated (p. 85, bottom). Regarding claim 134, Mills teaches truncated oligomannose glycans were detected at asparagines 19 and 270 (paragraph bridging pp. 87-88).

At the time of the invention it would have been obvious to one of ordinary skill in the art to combine the teachings of Roeber, Grueninger-Leitch, and Mills to practice the method of Grueninger-Leitch to deglycosylate Cerezyme® using PNGase with subsequent removal of PNGase. One would have been motivated to do this in order to

attempt improvement in crystal quality as taught by Grueninger-Leitch for crystallization as taught by Roeber to achieve a higher resolution of x-ray diffraction. One would have had a reasonable expectation of success to practice the method of Grueninger-Leitch to deglycosylate Cerezyme® using PNGase with subsequent removal of PNGase because of the teachings of Grueninger-Leitch and Mills. Therefore, the purified glucocerebrosidase solution, pharmaceutical composition, and article of manufacture of claims 129, 133-138, and 157-158 would have been obvious to one of ordinary skill in the art at the time of the invention.

According to MPEP 2112.01, "Where the claimed and prior art products…are produced by identical or substantially identical processes, a *prima facie* case of either anticipation or obviousness has been established. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977)". Since the Office does not have the facilities for examining and comparing applicants' purified glucocerebrosidase solution with that taught and/or suggested by the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the purified glucocerebrosidase solution of the prior art does not possess the same material structural and functional characteristics of the claimed purified glucocerebrosidase solution). See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald* et al., 205 USPQ 594.

Conclusion

[22] Status of the claims:

- Claims 123-124, 129, and 133-158 are pending the application.

- Claims 139-156 are withdrawn from consideration.

- Claim 123 is objected to for reasons noted above and claim 124 is objected to as being dependent upon claim 123. Claims 123-124 would be allowable if rewritten or amended to overcome the objection to claim 123 set forth in this Office action.

- Claims 129, 133-138, and 157-158 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Steadman whose telephone number is 571-272-0942. The examiner can normally be reached on Mon to Fri, 7:30 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath Rao can be reached on 571-272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/David J. Steadman/
Primary Examiner, Art Unit 1656